Remarks

Claims 40-54 are currently pending. Claims 43, 44, 46, 47, 50, and 51 have been withdrawn from consideration. Claim 40 has been amended to more clearly define the intended invention. New claim 54 is supported in the specification at Figure 2. The specification has been amended by substituting the sequence listing in both printed and computer readable form. No new matter has been added.

The Examiner objected to the amendment filed 1 February 1999 under 35 U.S.C. 132 on the grounds that it introduced new matter into the disclosure. For the reasons that follow, and as evidenced in the amended sequence listing and the attached Declaration of Amy S. Weiner, Applicants respectfully submit that the instant amendment does not introduce new matter into the disclosure and request that the instant amendment be entered accordingly. The Examiner also rejected the pending claims under 35 U.S.C. 112, first paragraph, on several grounds. Applicants respectfully traverse the objection, rejections, and accompanying remarks.

The Sequence Listing

This application is a Rule 1.62 continuation of application (serial no. 08/757,958), filed 25 November 1996 (the "parent"), which was a Rule 1.62 continuation of application (serial no. 08/061,699), filed 12 May 1993 (the "grandparent"). Prior to addressing the merits of the instant objection, Applications believe it would be helpful to briefly review the seven year history of this application.

The grandparent was initially filed without a sequence listing on 12 May 1993. Applicants filed a sequence listing via a preliminary amendment on 28 July 1993. On 10 November 1993, the Examiner issued a Notice to Comply with regard to sequence listing requirements, stating that each permutation of a variable sequence needed to be listed separately. Applicants responded on 10 January 1994, indicating that the Examiner's requirement would necessitate the listing of many more sequences than required by the Rules, and argued that such a requirement was unreasonable.

In a communication mailed 3 March 1994, the Examiner agreed that Applicants were "partially correct" and indicated that, among other things, Applicants should use "Xaa" in order to comply with the Rules.

Applicants filed a substitute sequence listing on 6 April 1994. This new sequence listing contained entries for each sequence in the disclosure of 4 or more nucleotides or amino acids, and made use of "Xaa" to indicate variability of amino acids in particular positions. For example, SEQ ID NO: 8 listed 31 amino acids, 10 of which were represented as "Xaa". The corresponding sequence in the disclosure, at Figure 2-1 line 1, was amended to include the designation of SEQ ID NO: 8.

The Examiner mailed a communication on 12 May 1994, requiring a new substitute sequence listing to fix an error in SEQ ID NO:2, which had used "Ahe" instead of "Xaa". Applicants filed a complying response on 24 May 1994.

The Examiner and Applicants' agent had a telephone conversation on 13 June 1994 in which Applicants' agent was informed that SEQ ID NO:2 needed to be amended again in order to list the amino acid length of the sequence as 32 amino acids rather than 31. Applicants filed a complying amendment on 16 June 1994.

In response to a restriction requirement mailed 15 August 1994, Applicants elected Group I, claims 1-12, directed to methods of passive immunization, rather than the immunogenic polypeptides claimed in the instant application, which ultimately were presented for examination in the parent of this application (08/757,958) by way of a preliminary amendment filed 31 January 1997. Unfortunately, a final office action was mailed 28 January 1997, without having received or entered the preliminary amendment as they crossed in the mail. Applicants then filed the instant application on 25 March 1997 with an identical preliminary amendment, canceling claims 1-39 and adding new claims 40-53 directed to immunogenic polypeptides.

The Examiner mailed a new communication on 19 August 1997 enclosing a new Notice to Comply directed at correcting several minor sequence listing problems, none of which were related to SEQ ID NO: 8. Applicants filed a response on 18 September 1997 rectifying the cited problems.

The Examiner then issued a Restriction Requirement, mailed 9 December 1997, requiring restriction to either Group I (claims 40 and 42-53) drawn to peptides and peptide compositions, or Group II (claim 41) drawn to a fusion peptide. The Examiner also required election of a species and subspecies if Applicants were to elect Group I. Applicants elected Group I by

response filed 8 January 1998, and elected species A (claims 42, 45, and 48-51), and subspecies A (claims 48-49). Applicants also argued for rejoining of claim 41 to Group I.

The Examiner mailed the next office action on 27 March 1998, in which he rejoined claim 41 to Group I, and withdrew from consideration claims 43, 44, 46, 47, 50 and 51. The Examiner also objected to the amendment filed 18 September 1997 as containing new matter in that SEQ ID NO: 8 used the symbol "Xaa" as intending to mean "unknown or other amino acid". The Examiner noted that Figure 2-1 did show a consensus sequence in the first line, which used "." in certain positions, but the Examiner believed it was not clear whether "." meant any amino acid or unknown amino acid.

Applicants first point out that SEQ ID NO: 8 was first submitted in its then present form more than three years earlier, in the amendment of 6 April 1994, and at that time had used the symbol "Xaa" as suggested by the Examiner in his communication. In any event, Applicants believed then and believe now that "any amino acid" is precisely what "." means, and that it is the only reasonable interpretation of the consensus sequence provided in Figure 2-1, as will be discussed more fully below.

Applicants' former attorney appreciated this significant point when she filed a response on 28 September 1998, amending SEQ ID NO: 8 to specify for each of the "Xaa" entries a list of amino acids culled from the 90 example sequences found in Figure 2. As stated in that response, Applicants believed there was sufficient support for the "." to be read as encompassing any amino acid, however, in the interests of expediting prosecution, the "Xaa" entries were being

amended to be limited to the specific examples cited. Unfortunately, prosecution was not expedited with those limitations, and the instant amendment to the sequence listing reverts back to the original meaning of the "." as filed in the first sequence listing containing SEQ ID NO: 8, filed 6 April 1994.

Applicants' former attorney did not file a computer readable form with its amendment, thus the Examiner mailed a communication on 18 December 1998 with a Notice to Comply requiring such a computer readable form. The undersigned provided the computer readable form by way of an amendment filed 28 January 1999.

The Examiner then mailed the pending final office action on 7 April 1999. Applicants filed a Notice of Appeal on 6 October 1999, and then filed the currently pending Continuing Prosecution Application (the "CPA"), on 6 April 2000.

The undersigned thanks the Examiner for the telephone conversations following the filing of the CPA, and for considering Applicants' arguments regarding the meaning of "." as it appears in Figure 2-1.

Figure 2-1 specifies in its first line that a "consensus" has a particular sequence, using the symbol "." in several positions. Where a specific letter appears in the consensus sequence, it is readily apparent that that letter appears in most of the 90 examples set forth in the remainder of Figure 2. The Applicants discerned the prevalence in those positions of particular amino acids, and thus deduced the consensus sequence from an analysis of those prevalencies. However, there were certain positions where no concensus was readily achievable because the variability of

the amino acids in those positions was too great. A symbol was needed to represent a lack of consensus, and the "." was ultimately used in the Figure.

It is admittedly unfortunate that a "." was used in the remainder of the Figure to show the presence of consensus, rather than its absence, however, that does not mean that the use of "." in the consensus sequence itself is any less clear.

Applicants also respectfully point out that what is at issue is simply the listing of the sequence in compliance with the Rules. The sequence is 31 amino acids in length, it has specific amino acids in certain positions, and in ten positions there is no amino acid listed. Where an amino acid is any amino acid or an unknown amino acid, the proper way to list it in a sequence listing is to use "Xaa" and that is what Applicants have done. A reasonable, realistic approach can lead only to this conclusion. Further, to interpret the "." to mean anything else requires a tortured meaning of "consensus".

The Examiner suggests alternative meanings of the "." symbol, but these alternatives are not supported by logic or common sense in the context of the disclosure, or also mandate the use of "Xaa" to mean any amino acid. The Examiner first suggests that "." might mean the variety of amino acids found in that position in the 90 example sequences. But, as the Examiner also points out, that would not allow for a possible sequence wherein the "." in the first position is defined as the amino acid found in the first example sequence, while the "." in the next undefined position is defined as the amino acid found in the second example, and so forth. The Examiner states that the specification does not disclose that the "." means "any amino acid." That is technically true,

but since a consensus sequence is by nature a sequence in which particular amino acids are conserved, it would be understood by any of skill in the art that the "." simply means "any amino acid".

The Examiner then wonders whether any particular amino acid was contemplated for the "." positions, or even if the "." only meant "a portion of the sequence that was generally more variable than other portions of the consensus sequence which were assigned a particular amino acid." Office Action at pages 2-3.

Applicants submit that these two interpretations are not mutually exclusive, and that in either case, the obvious way to write the consensus sequence would be to use some symbol, like a ".", because a specific letter would not be available. The consensus sequence had to be 31 amino acids in length, and had to have positions filled without using specific amino acids. The "." symbol is a simple method of denoting "any amino acid", all in an effort to indicate that at those positions there was no consensus.

Applicants provide the declaration of one of the inventors, Amy Weiner, attesting to the fact that the "." does in fact mean "any amino acid", and did so at the time of the filing of the application. In light of the Declaration and the foregoing arguments, Applicants respectfully request entry of the amendment to the specification substituting the sequence listing, and withdrawal of the objection to the sequence listing.

The Section 112 Rejections

In paragraph 4 of the Office Action, the Examiner rejected claims 40-42, 45, 48, 49, 52, and 53 under 35 U.S.C. 112, first paragraph on the grounds that Applicants did not have possession of the claimed invention because SEQ ID NO: 8, recited in claim 40, constitutes new matter. The arguments presented by the Examiner are identical to those set forth in the objection to the sequence listing, described above. Applicants respectfully disagree.

Claim 40 is directed to an immunogenic polypeptide comprising at least one copy of the consensus sequence of 31 amino acids, listed as SEQ ID NO: 8. As the foregoing discussion elaborated, the "." in the consensus sequence presented in Figure 2-1 is intended to mean "any amino acid" and the use of "Xaa" to so indicate is appropriate. The sequence presented in claim 40 is therefore not new matter, and this rejection should likewise be withdrawn.

In paragraph 5 of the Office Action, the Examiner rejected claims 40-42, 45, 48, 49, 52, and 53 under 35 U.S.C. 112, first paragraph on the grounds that Applicants did not have possession of the claimed invention because the Examiner believed the "wherein" clause found in claim 40 constitutes new matter. As amended, claim 40's amended "wherein" clause specifies that the immunogenic polypeptide comprises the consensus ("motif") sequence, but includes the limitation that there is no other HCV hypervariable region sequence contained in the immunogenic polypeptide. While this limitation is not specifically referred to in the specification; it is, nonetheless, inherent in the disclosure that the key immunogenic sequences of the invention are derived from the consensus sequence, and those sequences, if any, which are

derived from the hypervariable region of HCV but which do not display the consensus sequence are not considered valuable in the preparation of immunogenic polypeptides of the invention. In any event, if the broader language of the claim would be allowable without the limitation, surely the addition of such a limitation can not be said to destroy the patentability of the claim. Applicants respectfully request withdrawal of this rejection.

In paragraph 6 of the Office Action, the Examiner rejected claims 40-42, 45, 48, 49, 52, and 53 under 35 U.S.C. 112, first paragraph, on the ground that the claims contain subject matter not described so as to enable one skilled in the art to make and/or use the invention. Applicants disagree.

The crux of the Examiner's position revolves around the limitation that the polypeptide be "immunogenic", and the argument appears to be that the specification does not teach one of skill in the art how to figure out which polypeptides having the motif sequence according to the claims would be immunogenic.

The specification defines immunogenic as "the ability to elicit a cellular and/or humoral immune response." Specification at 14. On page 15, the specification describes generally that the desired polypeptides are expressed in prokaryotic or eukaryotic expression systems, and then purified. "Such polypeptides can be used as diagnostics, or those which give rise to neutralizing antibodies may be formulated into vaccines." Specification at 15, lines 26-27. It is true that the specification does not specifically describe how one of skill in the art determines whether a particular polypeptide is immunogenic, but that is because the techniques for determining

whether a polypeptide is immunogenic were well-known in the art. Instead, the specification discloses additional means of enhancing immunogenicity, such as linkage to a carrier (page 20), combination with other HCV subunit antigens (page 19), preparation with particle forming proteins (page 20-21), and conjugation to adjuvants (page 21). This enhancement necessarily presumes that one of skill in the art already knows how to test a polypeptide for immunogenicity: merely inject an animal and assay for the production of humoral or cellular immune response.

The Examiner dismisses the Chien et al. reference discussed in the previous Weiner declaration on the ground that the peptide is not encompassed by the formula recited by the claim. While it is true that the Chien peptide was 21 amino acids in length, rather than the 31 amino acids of the claimed invention, it is noteworthy that, properly aligned, the Chien peptide does not accord with the consensus sequence by only a single amino acid (the K in the third to last position). Contrary to the Examiner's assertion that the Chien et al. publication is irrelevant, the question of whether the Chien peptide falls within the scope of the claims is not the issue, and misses the point of the declaration. The critical point is that Chien et al. demonstrated that the peptide was cross reactive with 14 out of 17 isolates.

The Examiner stated that the Chien et al. and Hattori et al. references "refer to experiments performed with a single peptide derived from a single actual HCV strain." Dr. Chien's work was cited because it showed that a single peptide drawn from the HCV hypervariable region was sufficient to bind 14 of 17 serum samples. Dr. Chien's work, then, is a specific example of the more general Hattori et al. reference, which shows cross reactivity with

several peptides. Applicants also direct the Examiner's attention to Dr. Chien's work as shown in Attachment A of Dr. Weiner's declaration of 22 April 1997. There, Dr. Chien's group demonstrated that three different HCV hypervariable region peptides, two of which were drawn from a consensus sequence, while the third was an isolate specific peptide. The results showed that the consensus sequence peptides elicited a higher degree of cross-reactivity than the isolate specific peptide, leading to the conclusion that "broadly cross-reacting antibodies to the HVR1 [HCV-1 hypervariable region] can be induced by CSPs [consensus sequence peptides] and may enhance vaccine preparations." Thus, Dr. Chien's work fully supports the conclusion that consensus sequence peptides of the present invention would be both immunogenic and cross-reactive.

Regarding the Hattori et al. reference, Applicants respectfully disagree with the Examiner's assertion. Rather than using a single peptide from a single strain, Hattori et al. performed an experiment, among others, using five different fusion peptides, each of which cross reacted with a large percentage of sera from 108 patients. While the Examiner does not address the specifics of Hattori et al., it clearly demonstrated that sera from numerous HCV patients were particularly cross reactive with peptides from the HCV hypervariable region. At the very least these two documents indicate a strong likelihood that other peptides from this region would likewise be immunogenic and cross reactive as well.

In sum, one of skill in the art armed with the instant specification could readily practice the present invention. The skilled artisan could prepare an immunogenic polypeptide of the

claims, with no more than routine experimentation testing different polypeptides until obtaining an immunogenic one. The evidence of record even suggests the great likelihood of early success. The Examiner has not shown why this is not so. Applicants therefore request withdrawal of this rejection.

Conclusion

Applicants respectfully submit that the application is now in condition for allowance, and such action is requested. Should the Examiner have any comments, Applicants urge the Examiner to call the undersigned at the indicated phone number. Please continue to direct all correspondence relating to this application to:

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